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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,925	08/28/2001	James E. Dahlberg	FORS-06612	6817

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EXAMINER
SANDALS, WILLIAM O

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/940,925	Dahlberg et al.
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 14, 2003*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *71-94* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *71-94* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Aug 28, 2001* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *14*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

file 9
Aut #17

DETAILED ACTION

Status of the Claims

1. Claims 71-94 are pending. Claims 1-70 and 95-123 have been cancelled.

Priority

2. The priority claim has been amended in Paper No. 15, filed August 28, 2002. However, the priority claim has an element which is not clear. At lines 3-5 the priority claim states: "U.S. Application 08/520,946, filed January 15, 1998, which is a continuing application of U.S. Application 08/520,946, filed August 30, 1995". The portion of the above priority claim which reads "08/520,946, filed January 15, 1998, which is a continuing application of U.S. Application" is referring to the Continuing Prosecution Application, filed in January 15, 1998, and provides information which is not necessary to the priority claim and introduces some confusion as to the filing date status of U.S. Application 08/520,946. Correction of the priority claim by deletion of the reference to the Continuing Prosecution Application (CPA) filing date of January 15, 1998 is therefore required.

Claim Objections

3. Claim 84 is objected to because of the following informalities: at line 2 it states "derived from an organism from genus Thermus". Adding "the" before "genus" would correct the grammar of the phrase. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 71 (and dependent claims 72-94) and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. The preamble of claim 71 states at line 1 "[a] method of detecting a nucleic acid", and concludes at section "d)" "detecting the cleavage of said complex". The conclusion of the claim does not result in the stated intention of the preamble, and thus the claim is vague and indefinite.

7. Claim 94 recites the limitation "said duplex region" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 71-75, 77-81, 87, 88 and 92-94 are rejected under 35 U.S.C. 102(b) as being anticipated by US 4,994,368 (Goodman et al.).

Goodman et al. teach at the abstract a method of combining a cleavage means with a primary (target) nucleic acid sequence which is hybridized to two nucleic acid sequences (first and second nucleic acid sequences) (the hybridized nucleic acids result in a first complex) with the primary (target) nucleic acid having two adjacent regions for the detection of a polynucleotide analyte. The nucleic acid (first nucleic acid) which is hybridized to the (target) primary nucleic acid is cleaved to produce a product nucleic acid (first cleavage product) which is then hybridized to another nucleic acid sequence (the third nucleic acid sequence) to form a second complex. The second complex is then cleaved by the cleavage means to produce another cleavage product (second cleavage product = cleaved third nucleic acid). The second cleavage product is detected. The conditions for the method may be isothermal (see claim 10). The detection may comprise detection by fluorescence, mass, dye intercalation, staining or radioactivity (see column 19 and claims 16-17). The nucleic acids may be attached to a solid support (see column 20). The cleavage means is an enzyme. Each of the nucleic acids comprise a 3' terminus (see claims 6 and 18, and the summary of the invention). The cleavage of the third nucleic acid occurs within the (duplex) hybridized region.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 71-81, 87, 88 and 92-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,994,368 (Goodman et al.) in view of US 5,994,056 (Higuchi et al.).

The claims are drawn to a method of combining a cleavage means with a target nucleic acid sequence which is hybridized to first and second nucleic acid sequences to form a first complex (the target nucleic acid may comprise two adjacent hybridized regions). The hybridized first nucleic acid is cleaved to produce a first cleavage product. The first cleavage product is then hybridized to a third nucleic acid sequence to form a second complex. The second complex is then cleaved by the cleavage means to produce a second cleavage product (which may cleave the third nucleic acid). The second cleavage is detected. The second cleavage product may be detected (claim 72). The conditions for the method may be isothermal (claim 73). The detection may comprise detection by fluorescence, mass, dye intercalation, staining or radioactivity and fluorescence quenching (claims 74-77). The nucleic acids may be attached to a solid support (claims 78-80). The cleavage means may be an enzyme. The nucleic acids comprise a 3'

terminus. The cleavage of the third nucleic acid may occur within the duplex (hybridized) region.

Goodman et al. teach at the abstract a method of combining a cleavage means with a primary (target) nucleic acid sequence which is hybridized to two nucleic acid sequences (first and second nucleic acid sequences) (the hybridized nucleic acids result in a first complex) with the primary (target) nucleic acid having two adjacent regions. The nucleic acid (first nucleic acid) which is hybridized to the (target) primary nucleic acid is cleaved to produce a product nucleic acid (first cleavage product) which is then hybridized to another nucleic acid sequence (the third nucleic acid sequence) to form a second complex. The second complex is then cleaved by the cleavage means to produce another cleavage product (second cleavage product = cleaved third nucleic acid). The second cleavage product is detected. The conditions for the method may be isothermal (see claim 10). The detection may comprise detection by fluorescence, mass, dye intercalation, staining or radioactivity (see column 19 and claims 16-17). The nucleic acids may be attached to a solid support (see column 20). The cleavage means is an enzyme. The nucleic acids comprise a 3' terminus (see claims 6 and 18, and the summary of the invention). The cleavage of the third nucleic acid occurs within the (duplex) hybridized region.

Goodman et al. do not teach fluorescence quenching as a method of detection.

Higuchi et al. teach fluorescence quenching as an alternative to fluorescence detection or dye intercalation in a method of detecting nucleic acids, where a fluorescence quenching assay

minimizes or eliminates handling of the sample during the assay (see column 5, lines 53-63, column 6, lines 29-36 and line 54 bridging to column 7, line 14).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the method of nucleic acid cleavage and nucleic acid detection by fluorescence of Goodman et al. with the alternative method of detection by fluorescence quenching as taught by Higuchi et al. for the expected benefit of minimizing or eliminating sample handling in the detection assay. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Goodman et al. who teach a method of detection of a cleavage product by fluorescence, and the teachings of Higuchi et al. who demonstrate a method of detection of nucleic acids by fluorescence quenching.

12. Claims 71-88 and 92-94 rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,994,368 (Goodman et al.) in view of US 5,994,056 (Higuchi et al.) as applied to claims 71-81, 87, 88 and 92-94 above, and further in view of US 5,210,015 (Gelfand et al.).

The claims are drawn to the invention as described above and where the cleavage means comprises a 5' nuclease enzyme which is comprised in a thermostable DNA polymerase from an organism of the genus Thermus.

Goodman et al. and Higuchi et al. teach the invention as described above.

Goodman et al. and Higuchi et al. do not teach that the cleavage means comprises a 5' nuclease enzyme which is comprised in a thermostable DNA polymerase from an organism of the genus Thermus.

Gelfand et al. teach at column 2, and columns 6-7, a cleavage means which comprises a 5' nuclease enzyme which is comprised in a thermostable DNA polymerase from an organism of the genus Thermus used in a method of cleaving a first nucleic acid which has been hybridized to a target nucleic acid. The target nucleic acid is also hybridized to a second nucleic acid. The process is for the detection of the cleaved portion of the first nucleic acid. The target nucleic acid regions hybridized to the first and second nucleic acids are adjacent. The cleavage product nucleic acids are detected by fluorescence or by intercalating dyes. Gelfand et al. teach at column 6, lines 2-24, that the cleavage means used in the method is desirable since it is thermostable and may be used at higher temperatures (higher temperatures are used in the hybridization steps), without the loss of activity.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the method of nucleic acid cleavage and nucleic acid detection by fluorescence quenching of Goodman et al. and Higuchi et al. with the 5' nuclease enzyme which is comprised in a thermostable DNA polymerase from an organism of the genus Thermus used in a method of cleaving a first nucleic acid which has been hybridized to a target nucleic acid as taught by Gelfand et al. for the expected benefit of maintaining enzyme activity at the higher temperatures required for hybridization of the nucleic acids. Further, a person of ordinary skill in

the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Goodman et al., Higuchi et al. and Gelfand et al. who demonstrate a method of hybridizing, cleaving and detecting nucleic acids in a single reaction mixture.

13. Claims 71-94 rejected under 35 U.S.C. 103(a) as being unpatentable over Goodman et al.) in view of US 5,994,056 (Higuchi et al.) and further in view of US 5,210,015 (Gelfand et al.) as applied to claims 71-88 and 92-94 above, and further in view of US 4,935,357 (Szybalski).

The claims are drawn to the invention as described above and where the third nucleic acid comprises a hairpin structure having a single stranded 3' arm adjacent to the duplex region where the single stranded arm of the third nucleic acid hybridizes to the first cleavage product.

Goodman et al., Higuchi et al. and Gelfand et al. teach the invention as described above.

Goodman et al., Higuchi et al. and Gelfand et al. do not teach that the third nucleic acid has a hairpin structure with a 3' single stranded arm which hybridizes to the first cleavage product.

Szybalski teaches at the abstract and at the summary of the invention a nucleotide "adapter" comprising a hairpin structure with a single stranded 3' arm adjacent to the duplex region. The "adapter" facilitates cleavage of a single stranded target nucleic acid at a desired location by a cleavage means.

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to modify the method of hybridizing a nucleic acid to the cleavage product of the first nucleic acid complex and nucleic acid detection by fluorescence quenching as taught by Goodman et al., Higuchi et al. and Gelfand et al. by substituting the nucleotide "adapter" comprising a hairpin structure adjacent to a single stranded 3' arm (adjacent to the duplex region) as taught by Szybalski (the 3' single stranded arm of Szybalski will hybridize with the single stranded first cleavage product). One of ordinary skill in the art would have been motivated to make a substitution of the "adapter" of Szybalski for the expected benefit that the "adapter" facilitates cleavage of the single stranded nucleic acid (first cleavage product) at a desired location by a cleavage means. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Goodman et al., Higuchi et al. and Gelfand et al. who demonstrate a method of hybridizing, cleaving and detecting nucleic acids in a single reaction mixture.

Conclusion

14. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Tech Center customer service center at telephone number (703) 308-0198.

William Sandals, Ph.D.
Examiner
June 11, 2003

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